

## Adipose tissue related adipokines and cytokines regulate PCSK9 expression in HepG2 cells

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**Background:** Proprotein convertase subtilisin/kexin type 9 (PCSK9) represents a key-regulator pathway for hepatic LDL receptor degradation. Clinical and experimental evidence indicates that PCSK9 may be either a cause or an effect of MetS. PCSK9 levels correlate with MetS features, namely atherogenic dyslipidemia and insulin sensitivity indices. The aim was to study the possible molecular mechanisms linking the effects of cytokines (TNF- $\alpha$  and resistin) and adipokines (leptin) on PCSK9 expression and *de novo* lipogenesis. **Methods:** Human hepatocellular liver carcinoma cell line (HepG2) and HepG2 overexpressing PCSK9 (HepG2<sup>PCSK9</sup>) were used as *in vitro* tools. qPCR, Western blot, ELISA and luciferase reporter assays, together with siRNA directed to STAT3 and SOCS3, were used. **Results:** HepG2 expresses leptin (ObR1) and resistin (adenylyl cyclase-associated protein 1, CAP1) receptors. HepG2<sup>PCSK9</sup> expresses higher levels of ObR1 and CAP1. Twenty-four h treatment of HepG2 with TNF- $\alpha$  (10 ng/mL), and 48-h treatment with leptin (200 ng/mL) and resistin (50 ng/mL) induced the expression of both PCSK9 (2.3-, 2.0- and 3.5-fold, respectively) and SOCS3 (3-, 1.8- and 1.9-fold, respectively). TNF- $\alpha$  and leptin increased the secreting PCSK9 (+15% and +20%, respectively) but only leptin stimulated PCSK9 promoter activity (+20%). TNF- $\alpha$ , leptin and resistin induced the gene expression of sterol regulatory element-binding protein 1 (SREBP1), stearoyl-CoA desaturase-1 (SCD-1), fatty acid synthase (FAS) and microsomal triglyceride transfer protein (MTP). The TNF- $\alpha$  mediated effects were inhibited by transfection with siRNA anti-STAT3, suggesting the involvement of the JAK/STAT pathway.

**Conclusions:** Pro-inflammatory cytokines and adipokines up-regulate PCSK9 expression and the key genes involved in the *de novo* lipogenesis.